

**UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)***(Only for new nonprovisional applications under 37 CFR 1.53(b))*Docket No.
ARC2914C1Total Pages in this Submission
57**TO THE ASSISTANT COMMISSIONER FOR PATENTS**Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

STABLE NON-AQUEOUS SINGLE PHASE VISCOUS VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES

and invented by:

Berry et al.If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:☒ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No.: **09/497,422**

Which is a:

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☐ Specification having 35 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☒ Cross References to Related Applications *(if applicable)*
 - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
 - d. ☐ Reference to Microfiche Appendix *(if applicable)*
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☒ Brief Description of the Drawings *(if drawings filed)*
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure

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Application Elements (Continued)

3. ☒ Drawing(s) (when necessary as prescribed by 35 USC 113)
- a. ☐ Formal Number of Sheets _____
- b. ☒ Informal Number of Sheets 8
4. ☒ Oath or Declaration
- a. ☐ Newly executed (original or copy) ☒ Unexecuted
- b. ☐ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional application only)
- c. ☐ With Power of Attorney ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference (usable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all must be included)
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy (identical to computer copy)
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☒ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(B) Statement (when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☒ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class ☒ Express Mail (Specify Label No.): EL497409114US

UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

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Total Pages in this Submission

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

16. ☐ Additional Enclosures (please identify below):

Fee Calculation and Transmittal

CLAIMS AS FILED

| For | #Filed | #Allowed | #Extra | Rate | Fee |
|---|--------|----------|--------|-----------|------------|
| Total Claims | 41 | - 20 = | 21 | x \$22.00 | \$462.00 |
| Indep. Claims | 6 | - 3 = | 3 | x \$82.00 | \$246.00 |
| Multiple Dependent Claims (check if applicable) <input checked="" type="checkbox"/> | | | | | \$780.00 |
| BASIC FEE | | | | | \$790.00 |
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).


Signature

Pauline A. Clarke
Registration No.: 29,783

Dated: July 28, 2000

cc:

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)Applicant(s): **Berry et al.**

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Filing Date

Examiner

Group Art Unit

Invention:

STABLE NON-AQUEOUS SINGLE PHASE VISCOUS VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES

Utility Patent Application Transmittal; Photocopy of Specification, including claims, abstract and drawings; Photocopy of IDS; Unexecuted Declaration with Power of Attorney; Unexecuted Assignment; Postcard for Return

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STABLE NON-AQUEOUS SINGLE PHASE VISCOUS VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES

5

Cross-Reference to Related Applications

This application is a continuation-in-part application of US application Serial No. 09/497,422 filed February 3, 2000.

10

Field of the Invention

This invention relates to stable non-aqueous single phase biocompatible viscous vehicles capable of suspending beneficial agents and uniformly dispensing said agents at low flow rates and more particularly to stable uniformly mixed formulations of beneficial agents in stable non-aqueous single phase biocompatible viscous vehicles.

References

The following references are referred to by numbers in brackets ([]) at the relevant portion of the specification.

20

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7. Zhang, et al., *Pharm. Res.* **12**: 1447-1452 (1995).

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23. U.S. Patent 5,614,221
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25. U.S. Patent 5,300,302
- 10 26. U.S. Patent 4,588,614
27. U.S. Patent 4,310,516
28. U.S. Patent 5,635,213
29. EP 379,147

Background of the Invention

Peptides, polypeptides, proteins and other proteinaceous substances (e.g., viruses, antibodies) collectively referred to herein as proteins, have great utility as pharmaceuticals in the prevention, treatment and diagnosis of disease. Proteins are naturally active in aqueous environments, thus the preferred formulations of proteins have been in aqueous solutions. However, proteins are only marginally stable in aqueous solutions. Thus, protein pharmaceuticals often have short shelf-lives under ambient conditions or require refrigeration. Further, many proteins have only limited solubility in aqueous solutions. Even when they are soluble at high concentrations, they are prone to aggregation and precipitation.

Because proteins can easily degrade, the standard method for delivering such compounds has been daily injections. Proteins can degrade via a number of mechanisms, including deamidations of asparagine and glutamine; oxidation of methionine and, to a lesser degree, tryptophan, tyrosine and histidine; hydrolysis of peptide bonds; disulfide interchange; and racemization of chiral amino acid residues [1-7]. Water is a reactant in nearly all of these degradation pathways. Further, water acts as a plasticizer, which

facilitates unfolding and irreversible aggregation of proteins. Since water is a participant in almost all protein degradation pathways, reduction of aqueous protein solution to a dry powder provides an alternative formulation methodology to enhance the stability of protein pharmaceuticals.

5 One approach to stabilizing proteins is to dry them using various techniques, including freeze-drying, spray-drying, lyophilization, and desiccation. Dried proteins are stored as dry powders until their use is required.

10 A serious drawback to drying of proteins is that often one would like to use proteins in some sort of flowable form. Parenteral injection and the use of drug delivery devices for sustained delivery of drug are two examples of the applications where one would like to use proteins in a flowable form. For injection, dried proteins must be reconstituted, adding additional steps which are time-consuming and where contamination may occur, and exposing the
15 protein to potentially destabilizing conditions [7]. For drug delivery devices the protein formulations must be stable for extended periods of time at body temperature and maintain their flowability for the expected life of the device.

Solution formulations of proteins/peptides in non-aqueous polar aprotic solvents such as DMSO and DMF have been shown to be stable at elevated
20 temperatures for long periods of time [8]. However, such solvent based formulations will not be useable for all proteins since many proteins have low solubility in these solvents. The lower the solubility of the protein in the formulation, the more solvent would have to be used for delivery of a specific amount of protein. Low concentration solutions may be useful for injections,
25 but may not be useful for long term delivery at low flow rates.

Proteins have been formulated for delivery using perfluorodecalin [9, 10], methoxyflurane [9], high concentrations in water [11], polyethylene glycol [12], PLGA [13, 14], ethylenevinylacetate/polyvinylpyrrolidone mixtures [15], PEG400/povidone [16]. However, these formulations were not shown to
30 retain a uniform suspension of protein in viscous vehicle over long periods of time.

Many biologically active compounds degrade over time in aqueous solution. Carriers in which proteins do not dissolve but rather are suspended, can often offer improved chemical stability. Furthermore, it can be beneficial to suspend the beneficial agent in a carrier when the agent exhibits low solubility in the desired vehicle. However, suspensions can have poor physical stability due to settling and agglomeration of the suspended beneficial agent. The problems with non-aqueous carriers tend to be exacerbated as the concentration of the active compound is increased.

Dispersing powdered proteins or peptides in lipid vehicles to yield parenteral sustained release formulations has been investigated [17-21]. The vehicles used were either various vegetable (sesame, soy, peanut, etc.) or synthetic oils (e.g., Miglyol) gelled with aluminum fatty acid esters such as aluminum stearates (mono-, di- or tri-), or with a polyglycerol ester. Although theoretically these vehicles might preclude solution denaturation and protect the drug from aqueous chemical degradation, the vehicles themselves are unstable at higher temperatures. The storage of liquid vegetable oils at body temperatures results in the formation of reactive species such as free fatty acids and peroxides (a process which is accelerated by the presence of traces of various metal ions such as copper or iron which can leach from some implantable devices). These peroxides not only adversely affect protein stability [22] but would be toxic when delivered directly to, for example, the central nervous system of a human or animal.

The sustained delivery of drugs has many advantages. Use of implantable devices assures patient compliance, since the delivery device is tamper-proof. With one insertion of a device, rather than daily injections, there is reduced site irritation, fewer occupational hazards for practitioners improved cost effectiveness through decreased costs of equipment for repeated injections, reduced hazards of waste disposal, and enhanced efficacy through controlled release as compared with depot injection. The use of implantable devices for sustained delivery of a wide variety of drugs or other beneficial agents is well known in the art. Typical devices are described, for example, in U.S. Patents Nos. 5,034,229; 5,057,318;

5,110,596; and 5,782,396. The disclosure of each of these patents is incorporated herein by reference.

For drug delivering implants, dosing durations of up to one year are not unusual. Beneficial agents which have low therapeutic delivery rates are prime candidates for use in implants. When the device is implanted or stored, settling of the beneficial agent in a liquid formulation can occur. This heterogeneity can adversely affect the concentration of the beneficial agent dispensed. Compounding this problem is the size of the implanted beneficial agent reservoir. Implant reservoirs are generally on the order of 25-250 μ l, but can be up to 25 ml.

Viscous formulations have been prepared using two separate components to be mixed with drug at use [23], thickening agents added to aqueous compositions [24], gelling agents added to aqueous drug solutions [25], porous textile sheet material [26], thickening agents with oleaginous material [27], viscous aqueous carrier for limited solubility drug [28], and extrudable elastic gels [29]. However, these formulations are mixed at use, contain aqueous components, use sheet matrices, or are delivered topically, orally, or intraduodenally.

Stability of formulations can be enhanced by freeze-drying, lyophilizing or spray-drying the active ingredient. The process of drying the active ingredient includes further advantages such as compounds which are relatively unstable in aqueous solution can be processed and filled into dosage containers, dried without elevated temperatures, and then stored in the dry state in which there are relatively few stability problems.

Pharmaceutical formulations, particularly parenteral products, should be sterilized after being sealed in the final container and within as short a time as possible after the filling and sealing have been completed. (See, for example Remington, Pharmaceutical Sciences, 15th ed. (1975)). Examples of sterilization techniques include thermal or dry-heat, aseptic, and ionized radiation. Combinations of these sterilization procedures may also be used to produce a sterile product.

There is a need to be able to deliver protein compositions to the body which are stable at body temperatures over extended periods of time to enable long term delivery of the protein. There is a need to be able to deliver concentrations of proteins that are efficacious. There is a need for a novel
5 non-aqueous formulation capable of homogeneously suspending proteins and dispensing such agents at body temperatures and low flow rates over extended periods of time.

Summary of the Invention

10 The present invention provides stable single phase non-aqueous biocompatible viscous vehicles capable of forming uniform suspensions with proteins. The components of the viscous vehicle comprise at least two of polymer, surfactant, and solvent. The ratios of the components will vary depending on the molecular weight of the components and the desired
15 viscosity of the final vehicle. Presently preferred component ratios are: polymer, about 5% to about 60%; solvent, about 5% to about 60%; and surfactant, about 5% to about 40%.

The present invention also provides stable formulations in which beneficial agents are uniformly suspended in stable single phase non-
20 aqueous biocompatible viscous vehicles. In particular, the beneficial agents are formulated in the viscous vehicles at concentrations of at least about 0.1%, depending upon the potency of the beneficial agent. These stable formulations may be stored at the temperature appropriate for the beneficial agent, ranging from cold, to body temperature (about 37°C) for long periods of
25 time (1 month to 1 year or more). In a preferred embodiment the formulation comprises about 0.1 to 50% (w/w) of beneficial agent, depending on the potency of the beneficial agent, the duration of treatment, and the rate of release for the drug delivery system.

These formulations are especially useful in implantable delivery
30 devices for long term delivery (e.g., 1 to 12 months or longer) of beneficial agent at body temperature, preferably about 37°C. Thus, the present invention also provides for the delivery of said proteins to the body over

extended period of time to enable long term delivery of the protein at low flow rates of about 0.3 to 100 $\mu\text{l/day}$, preferably about 0.3 to 4 $\mu\text{l/day}$ for about a 6 month delivery period and preferably 5 to 8 $\mu\text{l/day}$ for about a 3 month delivery period.

5 In another aspect, the invention provides methods for preparing stable non-aqueous biocompatible formulations of a beneficial agent in a single phase viscous vehicle. Preferred formulations comprise about 0.1 to 50% (w/w) beneficial agent depending on the potency of the beneficial agent, the duration of treatment, and the rate of release from the delivery system.

10 In yet a further aspect, the invention provides methods for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent, said methods comprising administering to said subject an effective amount of a stable non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a single phase viscous vehicle.

15 A further aspect of the invention is that non-aqueous single phase viscous vehicles containing beneficial agents are chemically and physically stable over a broad temperature range for long periods of time. The beneficial agents in the viscous vehicles are also chemically and physically stable over a broad temperature range for long periods of time. Thus, these formulations
20 are advantageous in that they may be shipped and stored at temperatures below, at, or above room temperature for long period of time. They are also suitable for use in implantable delivery devices in which the formulation must be stable at body temperature for extended periods of time.

The formulations of the present invention also remain stable when
25 delivered from implantable drug delivery systems. The beneficial agents have been shown to exhibit zero order release rates when delivered from implantable drug delivery systems at very low flow rates over extended periods of time.

30 Brief Description of the Drawings

Figure 1 shows the stability of hGH formulations of the present invention as determined at 37°C by reverse phase HPLC.

Figure 2 shows the stability of hGH formulations of the present invention as determined at 37°C by size exclusion chromatography.

Figure 3 shows the average release rate ($\mu\text{l/day}$) of 10% (w/w) spray-dried lysozyme in formulations of the present invention.

5 Figure 4 shows the average release rate ($\mu\text{l/day}$) of 10% (w/w) spray-dried hGH in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Figure 5 shows the average release rate ($\mu\text{g/day}$) of 10% lysozyme in a lauryl alcohol/polyvinylpyrrolidone vehicle.

10 Figure 6 shows the average release rate ($\mu\text{g/day}$) of 25% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Figure 7 shows the average release rate ($\mu\text{g/day}$) of 33% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

15 Figure 8 shows the average release rate ($\mu\text{g/day}$) of 45% lysozyme in a glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone vehicle.

Detailed Description of the Invention

The present invention is drawn to the unexpected discovery that uniformly suspending beneficial agents in non-aqueous single phase biocompatible viscous vehicles results in stable formulations which can be delivered at body temperature over an extended period of time at low flow rates. Previously known formulations of beneficial agents which are buffered aqueous or non-aqueous solutions which may or may not contain excipients do not provide formulations which can be uniformly dispensed at body temperatures at low flow rates over an extended period of time without exhibiting unacceptable amounts of aggregation or degradation of the formulation. The presently claimed formulations stabilize beneficial agents and can be stored at the temperature appropriate for the beneficial agent. The temperatures can range from cold (not exceeding 8°C) to body temperature (about 37°C) for long periods of time. These formulations are especially useful in implantable delivery devices for long term delivery (e.g., 1

to 12 months or longer) of drug at low flow rates and at body temperature, preferably about 37°C.

Standard beneficial agent formulations consist of dilute aqueous or non-aqueous solutions or suspensions. Drug stability is usually achieved by varying one or more of the following: pH, buffer type, ionic strength, excipients (EDTA, ascorbic acid, etc.) For these formulations, degradation pathways requiring water (hydrolysis, deamidation, racemization) cannot be fully stabilized. In the present invention, beneficial agents formulated in non-aqueous biocompatible single phase viscous vehicles containing for example, polyvinylpyrrolidone, vinyl acetate, and/or polyoxyethylenepolyoxypropylene block copolymers were shown to be chemically and physically stable. The viscosity of the formulation will depend upon a number of criteria, including the beneficial agent potency and concentration, and the process by which the formulation is prepared. The viscosity of the formulation can be chosen so that the desired amount of beneficial agent is delivered over the desired period of time.

The invention also consists of non-aqueous single phase biocompatible viscous vehicles capable of uniformly suspending beneficial agents and formulations containing at least one beneficial agent uniformly suspended in said viscous vehicle. The invention also consists of formulations containing at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle, which formulations are stable for an extended period of time at body temperatures, and capable of delivering said beneficial agents uniformly at low flow rates. The discovery consists of the realization that stable non-aqueous viscous vehicles improve the stability of beneficial agents in a wide range of formulation conditions including concentration, elevated temperatures and duration of stable formulation, thus making possible the delivery of beneficial agents in long term implantable devices that would not otherwise be feasible.

Definitions

As used herein, the following terms have the following meanings:

The term "chemical stability" means that an acceptable percentage of degradation products produced by chemical pathways such as oxidation, deamidation, or hydrolysis is formed. In particular, a formulation is considered chemically stable if no more than about 35% breakdown products are formed after 2 months at 37°C.

The term "physical stability" means that an acceptable percentage of aggregates (e.g., dimers, trimers and larger forms) are formed by the beneficial agent. For the formulation (viscous vehicle and beneficial agent) this term means that the formulation retains stability, flowability, and the ability to uniformly dispense the beneficial agent. In particular, a formulation is considered physically stable if no more than about 15% aggregates are formed after two months at 37°C.

The term "stable formulation" means that at least about 65% chemically and physically stable beneficial agent remains after two months at 37°C (or equivalent conditions at an elevated temperature). Particularly preferred formulations are those which retain at least about 80% chemically and physically stable beneficial agent under these conditions. Especially preferred stable formulations are those which do not exhibit degradation after sterilizing irradiation (e.g., gamma, beta or electron beam).

The term "beneficial agent" means peptides, proteins, nucleotides, hormones, viruses, antibodies, etc. that comprise polymers of amino acid or nucleic acid residues. These beneficial agents are generally degradable in water and generally stable as a dry powder at elevated temperatures. Synthetically produced, naturally derived or recombinantly produced moieties are included in this term. The term also includes lipoproteins and post translationally modified forms, e.g., glycosylated proteins. Analogs, derivatives, agonists, antagonists and pharmaceutically acceptable salts of any of these are included in this term. The term also includes proteins and/or protein substances which have D-amino acids, modified, derivatized or non-naturally occurring amino acids in the D- or L- configuration and/or peptomimetic units as part of their structure. The term protein will be used in

the present invention. The term also means that the beneficial agent is present in the solid state, e.g., powder or crystalline.

The term “excipient” means a more or less inert substance in a formulation that is added as a diluent or vehicle or to give form or consistency.

Excipients are distinguished from solvents such as ETOH, which are used to dissolve drugs in formulations. Excipients include non-ionic surfactants such as polysorbates, which are used to solubilize drugs in formulations; preservatives such as benzyl alcohols or methyl or propyl parabens, which are used to prevent or inhibit microbial growth; chelating agents; flavoring agents; and other pharmaceutically acceptable formulation aides.

The term "viscous vehicle" means a vehicle with a viscosity in the range of about 1,000 to 10,000,000 poise. The term includes Newtonian and non-Newtonian materials. Preferred are vehicles with a viscosity of about 10,000 to 250,000 poise. The formulations of this invention can uniformly expel beneficial agents suspended in the viscous vehicle from implantable drug delivery devices. The formulations exhibit a shear rate at the exit of said devices of 1 to 1×10^{-7} reciprocal second, preferably an exit shear rate of 1×10^{-2} to 1×10^{-5} reciprocal second.

The term “single phase” means a solid, semi-solid, or liquid homogeneous system that is both physically and chemically uniform throughout as determined by differential scanning calorimetry (DSC). The DSC scan should show one peak indicative of a single phase.

The term “biocompatible” means a property or characteristic of a viscous vehicle to disintegrate or break down, over a prolonged period of time, in response to the biological environment in the patient, by one or more physical or chemical degradative processes, for example by enzymatic action, oxidation or reduction, hydrolysis (proteolysis), displacement, e.g. ion exchange, or dissolution by solubilization, emulsion or micelle formation, and which material is then absorbed by the body and surrounding tissue, or otherwise dissipated thereby.

The term “polymer” includes polyesters such as PLA (polylactic acid) [having an inherent viscosity in the range of about 0.5 to 2.0 i.v.] and PLGA

(polylacticpolyglycolic acid) [having an inherent viscosity in the range of about 0.5 to 2.0 i.v.], pyrrolidones such as polyvinylpyrrolidone (having a molecular weight range of about 2,000 to 1,000,000), esters or ethers of unsaturated alcohols such as vinyl acetate, and polyoxyethylenepolyoxypropylene block copolymers (exhibiting a high viscosity at 37°C) such as Pluronic 105. Currently preferred polymer is polyvinylpyrrolidone.

The term "solvent" includes carboxylic acid esters such as lauryl lactate, polyhydric alcohols such as glycerin, polymers of polyhydric alcohols such as polyethylene glycol (having a molecular weight of about 200 to 600), fatty acids such as oleic acid and octanoic acid, oils such as castor oil, propylene carbonate, lauryl alcohol, or esters of polyhydric alcohols such as triacetin acetate. Currently preferred is lauryl lactate.

The term "surfactant" includes esters of polyhydric alcohols such as glycerol monolaurate, ethoxylated castor oil, polysorbates (for example Polysorbate 80), esters or ethers of saturated alcohols such as myristyl lactate (Ceraphyl 50), and polyoxyethylenepolyoxypropylene block copolymers such as Pluronic (for example, F68). Currently preferred are glycerol monolaurate and polysorbates.

The term "antioxidant" means a pharmaceutically acceptable aid for stabilization of the beneficial agent against degradation such as oxidation. Antioxidants include, but are not limited to, tocopherol (vitamin E), ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate. A preferred antioxidant depends on solubility and the efficiency of the antioxidant for protecting against degradation or chemical change of the beneficial agent in the preferred vehicle. Currently preferred is ascorbyl palmitate.

Preparation of Formulations

The present invention is drawn to stable non-aqueous single phase biocompatible viscous vehicles capable of suspending beneficial agents and uniformly dispensing said beneficial agents at body temperatures at low flow rates over an extended period of time. The present invention is also directed

to formulations containing beneficial agents uniformly suspended in said single phase biocompatible viscous vehicles which are stable for prolonged periods of time at body temperatures.

Examples of beneficial agents that may be formulated using the present invention include those peptides or proteins that have biological activity or that may be used to treat a disease or other pathological condition. They include, but are not limited to, adrenocorticotrophic hormone, angiotensin I and II, atrial natriuretic peptide, bombesin, bradykinin, calcitonin, cerebellin, dynorphin N, alpha and beta endorphin, endothelin, enkephalin, epidermal growth factor, fertirelin, follicular gonadotropin releasing peptide, galanin, glucagon, GLP-1, gonadorelin, gonadotropin, goserelin, growth hormone releasing peptide, histrelin, human growth hormone, insulin, interferons, leuprolide, LHRH, motilin, nafarerlin, neurotensin, oxytocin, relaxin, somatostatin, substance P, tumor necrosis factor, triptorelin, vasopressin, growth hormone, nerve growth factor, blood clotting factors, ribozymes, and antisense oligonucleotides. Analogs, derivatives, antagonists agonists and pharmaceutically acceptable salts of the above may also be used.

The beneficial agents useful in the formulations and methods of the present invention can be used in the form of a salt, preferably a pharmaceutically acceptable salt. Useful salts are known to those of skill in the art and include salts with inorganic acids, organic acids, inorganic bases, or organic bases.

Beneficial agents that are not readily soluble in non-aqueous solvents are preferred for use in the present invention. One of skill in the art can easily determine which compounds will be useful on the basis of their solubility. The amount of beneficial agent may vary depending on the potency of the compound, the condition to be treated, the solubility of the compound, the expected dose and the duration of administration. (See, for example, Gilman, et. al, The Pharmacological Basis of Therapeutics, 7th ed. (1990) and Remington, Pharmacological Sciences, 18th ed. (1990), the disclosures of which are incorporated herein by reference.)

It has been unexpectedly found that using a stable non-aqueous single phase biocompatible viscous vehicle increases the stability of the beneficial agent. For example, as seen in Figures 1 and 2, human growth hormone (hGH) was found to be stable at 37°C over 12 weeks in formulations of polyvinylpyrrolidone/PEG; Pluronic; and glycerol monolaurate/lauryl lactate/polyvinylpyrrolidone. Figure 1 shows stability results using reverse phase HPLC. Figure 2 shows stability results using size exclusion chromatography.

Generally, stable non-aqueous single phase biocompatible viscous vehicles may be prepared by combining the dry (low moisture content) ingredients in a dry box or under other dry conditions and blending them at elevated temperature, preferably about 40 to about 70°C, to allow them to liquify. The liquid vehicle is allowed to cool to room temperature. Differential scanning calorimetry was used to verify that the vehicle was single phase. The final moisture content of the viscous vehicle was <2%.

Generally, the stable formulations of the present invention may be prepared by combining the vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature, preferably about 40 to about 70°C, to disperse the beneficial agent uniformly throughout the vehicle. The formulation is allowed to cool to room temperature.

It has been found that drying the beneficial agent prior to formulation enhances the stability of the formulation.

It has also been found that adding antioxidants, such as tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate reduces the formation of degradation products (e.g., unstable chemical intermediates) during sterilization.

Methodology

We have found that stable non-aqueous beneficial agent formulations utilizing viscous vehicles may be prepared by combining the ingredients for the viscous vehicle under dry conditions and blending them at elevated temperature to allow them to liquify and form a single phase. Once a single phase viscous vehicle is formed, the vehicle is allowed to cool to room

temperature. Beneficial agent is added with mixing at elevated temperature under vacuum to uniformly disperse it in the viscous vehicle.

We have tested these beneficial agent formulations, for example formulations of hGH, for stability by subjecting them to accelerated aging tests. Results show that these formulations remained stable over extended periods of time.

We have tested beneficial agent formulations, for example human growth hormone and lysozyme, for stability by suspending them in a variety of non-aqueous single phase viscous vehicles prepared according to the present invention, then subjecting them to accelerated aging at elevated temperatures. The stability of the formulations was measured. Results of these studies demonstrate that these formulations were stable at conditions that approximate or exceed storage for one year at 37°C.

We have also tested beneficial agent formulations prepared as described herein for stability after 2.5 megarads gamma irradiation. Results show that these formulations remained chemically and physically stable after such irradiation.

Methods

The following methods were used to perform the studies in the Examples that follow.

1. Preparing Protein powders

Human Growth Hormone (obtained for example, from BresaGen Limited, Adelaide, Australia)

The active agent was reconstituted in deionized water. The solution containing the active agent was buffer exchanged using an Amicon Diaflo® Ultrafiltration membrane (molecular weight cut-off 10,000).

The diafiltrated active agent solution was spray dried using a Yamato mini-spray dryer. Powder was collected in a collection vessel through a cyclone trap. All handling of the spray dried powder took place in a dry box evacuated with nitrogen. The generated powder was analyzed for particle

size and distribution, moisture content, protein content and stability by size exclusion and reverse-phase chromatography.

It is known that the conformation of some proteins can be stabilized by the addition of a sugar (such as sucrose or mannitol) or a polyol (such as ethylene glycol, glycerol, glucose, and dextran.)

2. Preparation of Viscous Vehicles

We have found that stable single phase biocompatible viscous vehicles may be prepared by combining the ingredients and blending them at elevated temperatures to allow them to liquify and form a single phase. A differential scanning calorimetry scan showed one peak, indicative of a single phase. The mixing was completed under vacuum to remove trapped air bubbles produced from the powders. The mixer was a dual helix blade mixer (D.I.T.) which runs at a speed around 40 rpm. Higher speeds can be used but are not required.

If a three component viscous vehicle is prepared, the solvent portion of the vehicle was added to the heated bowl of the mixer first, followed by the surfactant. The polymer was added last, and the ingredients were mixed until a solution (single phase) resulted. Vacuum was applied during mixing to remove air bubbles. The solution was dispensed from the bowl while at elevated temperature, and allowed to cool to room temperature. On cooling the vehicle exhibited increased viscosity. Two and single component gels were made using the same process.

3. Preparation of beneficial agent formulations

To prepare the formulation, the single phase viscous vehicle was heated and then blended under vacuum with a weighed amount of beneficial agent. The beneficial agent and the single phase viscous vehicle were blended in the same manner as the vehicle was prepared, using a dual helix blade mixer (or other similar mixer). Mixing speed was between 40 and 120 rpm for approximately 15 minutes or until a uniform dispersion was attained. The resulting mixture was removed from the mixer, sealed in a dry container, and allowed to cool to room temperature.

4. Preparation of reservoirs

The reservoirs of implantable drug delivery devices (as disclosed in U.S. Patent Application Serial No. 08/595,761, incorporated herein by reference) were filled with the appropriate hGH formulation. The formulation
5 was filled into titanium reservoirs with a polymer plug blocking each end. The filled reservoir was then sealed in a polyfoil bag and placed in a stability testing oven.

It should be noted that the formulations in the reservoirs of these devices are completely isolated from the outside environment.

10

5. Reverse Phase-HPLC (RP-HPLC)

All stability samples of hGH were assayed for protein content and chemical stability by reverse phase chromatography (RP-HPLC). Analyses were performed on a Hewlett Packard HP-1090 system with a refrigerated
15 autosampler (4°C). The chromatographic conditions used are listed below.

TABLE 1
RP-HPLC Chromatographic Conditions

| Description | Parameter |
|-------------|-----------------------------|
| 20 | Column |
| | J.T. Baker-C18, 4.6x250 mm |
| | Flow Rate |
| | 1.0 mL/min |
| | Detection |
| | 214 nm |
| | Mobile Phase |
| | A: 0.1% TFA in water |
| | B: 0.1% TFA in acetonitrile |
| 25 | Gradient |
| | <u>time %A %B</u> |
| | 0 65 35 |
| | 5 50 50 |
| | 45 35 65 |
| | 50 30 70 |
| 30 | 55 65 35 |

An hGH reference standard solution was prepared and its protein content calculated from the absorbance measurement at 280 nm. Three dilutions of this solution, representing 80%, 100%, and 120% of the expected concentration of hGH in the samples were run in duplicate at the beginning and the end of each run and used to calculate total protein content of the samples.

6. Size Exclusion Chromatography (SEC)

All stability samples of hGH were assayed for protein content and high molecular weight degradation products by size exclusion chromatography. Analyses were performed on a Hewlett Packard HP-1090 system with a refrigerated autosampler (4°C). The chromatographic conditions used are listed below

TABLE 2
SEC Chromatographic Conditions

| Description | Parameter |
|--------------|--|
| Column | TSK-2000SWXL |
| Flow Rate | 0.5 ml/ min |
| Detection | 214 nm |
| Mobile Phase | 25 mM sodium phosphate, 100 mM sodium chloride, pH 7.0 |

A hGH reference standard solution was prepared and its protein content calculated from the absorbance measurement at 280 nm. Three dilutions of this solution, representing 80%, 100%, and 120% of the expected concentration of hGH in the samples were run in duplicate at the beginning and the end of each run and used to calculate total protein content of the samples. The amount of high molecular weight degradation products was calculated by area normalization.

The following examples are offered to illustrate this invention and are not meant to be construed in any way as limiting the scope of this invention.

EXAMPLE 1

Preparation of Non-aqueous Single Phase Viscous Vehicles

The non-aqueous single phase viscous vehicles can be prepared as follows and shown in the below table

- 5
- A. Glycerol monolaurate (Danisco Ingredients, New Century, Kansas) (25 g) was dissolved in lauryl lactate (ISP Van Dyk Inc., Belleville, NJ) (35 g) at 65°C. Polyvinylpyrrolidone C30 (BASF, Mount Olive, NJ) (40 g) was added and the mixture blended at about 40 rpm in a dual helix blade mixer (D.I.T.) until a single phase was achieved. Trapped air bubbles were removed by applying vacuum to the mixing chamber. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 10
- B. Glycerol monolaurate (Danisco Ingredients, New Century, Kansas) (25 g) was dissolved in lauryl lactate (ISP Van Dyk Inc., Belleville, NJ) (35 g) at 65°C. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (40 g) was added and the mixture blended at about 40 rpm in a dual helix blade mixer (D.I.T.) until a single phase was achieved. Trapped air bubbles were removed by applying vacuum to the mixing chamber. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 15
- 20
- C. Polyvinylpyrrolidone C30 (BASF, Mount Olive, NJ) (50 g) was dissolved in polyethylene glycol 400 (Union Carbide) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 25
- D. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in polyethylene glycol 400 (Union Carbide) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 30

- 5 E. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in castor oil (Spectrum, Gardena, CA) (50 g) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 10 F. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in octanoic acid (Spectrum, Gardena, CA) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 15 G. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (50 g) was dissolved in oleic acid (Spectrum, Gardena, CA) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 20 H. Polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (35%) was dissolved in glycerin (Baker, NJ) (65%) at approximately 65°C until a single phase solution was formed. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- I. Cremophor EL (ethoxylated castor oil) (BASF, Mount Olive, NJ) (5%) was dissolved in castor oil (Spectrum, Gardena, CA) (70%), and polyvinylpyrrolidone C17 (BASF, Mount Olive, NJ) (25%) was added and dissolved by mixing at approximately 40 rpm to form a single phase vehicle. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 25 J. Pluronic 105 (BASF, Mount Olive, NJ) was heated to approximately 65°C with mixing until melted. The single phase vehicle was dispensed from the mixer, and allowed to cool to room temperature.
- 30 K. Pluronic F68 (BASF, Sigma) 10% w/w and butylhydroxytoluene (Spectrum) 1% w/w were dissolved in 49% w/w propylene carbonate (Aldrich) by mixing under vacuum at 60°C until the materials dissolved. The vacuum was released, and the resulting liquid was added to 40% w/w poly lactic acid [poly(D,L-lactide), Resomer R207, Boehringer

5

10

[illegible]

Table 3
Component Ratios

| | Polymer | Component | | Ratio | Viscosity at Low |
|----|-----------|----------------|---------------|-----------|--------------------|
| | | Surfactant | Solvent | | Shear Rate (Poise) |
| 5 | PVP | GML | LL | 53:5:42 | 25,000 |
| | PVP | GML | LL | 55:10:35 | 50,000 |
| | PVP | GML | LL | 50:15:35 | 7,000 |
| | PVP | ---- | LA | 60:40 | |
| | PVP | Ceraphyl 50 | LA | 60:10:30 | |
| 10 | PVP | ---- | oleic acid | 50:50 | 30,000 |
| | PVP | ---- | octanoic acid | 55:45 | 7,000 |
| | PVP | polysorbate 80 | ---- | 50:50 | |
| | PVP | ---- | PEG 400 | 50:50 | |
| | PVP | castor oil | ---- | 50:50 | |
| 15 | ---- | Pluronic 105 | ---- | 100 | 1,000,000 |
| | PVP | ---- | glycerin | 50:50 | 5,000 |
| | PLA | F68 | PC | 30:10:60* | |
| | PVP (C17) | ML | LA | 50:25:25 | |
| | PVP (C17) | polysorbate 80 | LL | 55:40:5 | |

Wherein:

GML = glycerol monolaurate

LL = lauryl lactate

PVP = polyvinylpyrrolidone C30

LA = lauryl alcohol

PEG = polyethyleneglycol 400

F68 = poly(propylene oxide)/poly(ethylene oxide) block copolymer (a Member of the Pluronic family)

PC = propylene carbonate

PLA = poly lactic acid

ML = myristyl lactate

* also contains 1% butylhydroxytoluene

EXAMPLE 2

Preparation of hGH

5 A. Preparation by spray drying

Lyophilized hGH (BresaGen Limited, Adelaide, Australia) was reconstituted in 150 ml of deionized water. This stock solution contained 1050 mg of hGH. Buffer exchange was accomplished using an Amicon Diaflo® Ultrafiltration membrane (molecular weight cut-off 10,000). The
10 ultrafiltration cell was connected to an auxilliary reservoir containing 5mM phosphate buffer (pH 7). The cell's fluid volume, as well as the hGH concentration, remained constant as excipients were replaced by phosphate buffer.

The diafiltrated protein solution (protein concentration in the solution
15 approximately 2%) was spray dried using a Yamato mini-spray dryer. Settings on the spray dryer were as follows: aspiration pressure constantly adjusted to 1.3 kgf/cm², inlet temperature 120°C, solution flow rate 2.5 (approximately 3 ml/min). Powder was collected in a collection vessel through a cyclone trap. All handling of the spray dried powder took place in a dry box
20 evacuated with nitrogen (% RH: 1-4%). The water content of the suspending vehicles is shown in the below table.

TABLE 4
WATER CONTENT OF SUSPENDING VEHICLES

| Vehicle | Water Content of Vehicle at T 0 % w/w | Water Content of Vehicle in 12 wks. At 37°C % w/w |
|--------------|---|---|
| Pluronic 105 | 0.25 | 0.4 |
| GML/LL/PVP | 1.5 | 1.3 |
| PVP/PEG | 2.0 | 2.0 |

Wherein:

GML = glycerol monolaurate

LL = lauryl lactate

PVP = polyvinylpyrrolidone C30

PEG = polyethyleneglycol 400

EXAMPLE 3

Preparation of hGH Formulation

A portion of the single phase viscous vehicle was weighed (9 g) and heated to 60°C. hGH (BresaGen Limited, Adelaide, Australia) (1 g) was added to the vehicle and mixed for 15 minutes. The mixing was completed under vacuum to remove air bubbles added from the powder.

Approximately 10 mg of the spray-dried hGH powder were weighed out (content of hGH in the powder was recalculated based on the determined water and salt content) and mixed with 100 µl of the vehicle at 55-65°C (3 samples per each vehicle). Special care was taken while mixing powder in the suspending vehicle to achieve maximum particle uniform dispersion in the vehicle. All steps were done in a dry box.

The resulting suspension was dissolved with 10 ml of release rate buffer and analyzed by size exclusion and reverse-phase chromatography. Spray dried hGH powder was used as a control.

TABLE 5

STABILITY OF hGH SUSPENSIONS AT 37°C AS MEASURED BY
SIZE EXCLUSION CHROMATOGRAPHY

| | Time Weeks | Spray-dried Powder -80°C %LS | PVP/PEG 400 suspension %LS | GML/LL/PVP suspension %LS | Pluronic 105 suspension %LS |
|----|---------------|------------------------------------|----------------------------------|---------------------------------|-----------------------------------|
| 5 | | | | | |
| 10 | 0 | 96±1 | 88±6 | 92±2 | 87±7 |
| | 1 | 99±8 | 81±2 | 94±3 | 93±3 |
| | 2 | 99±3 | 83±1 | 97±1 | 94±1 |
| | 3 | 97±1 | 84±2 | 95±2 | 95±3 |
| | 4 | 95±2 | 82±8 | 94±4 | 93±5 |
| 15 | 7 | 95±4 | 76±3 | 93±4 | 88±2 |
| | 12 | 97±4 | 79±3 | 97±1 | 95±6 |

Each data point represents the mean ± relative standard deviation of
three individual samples taken from three separate vials.

20

TABLE 6
STABILITY OF hGH SUSPENSIONS at 37°C AS MEASURED BY
REVERSE PHASE CHROMATOGRAPHY

| | Time Weeks | spray-dried Powder -80°C %LS | PVP/PEG 400 suspension %LS | GML/LL/PVP suspension %LS | Pluronic 105 suspension %LS |
|----|---------------|------------------------------------|----------------------------------|---------------------------------|-----------------------------------|
| 5 | 0 | 104±1 | 99±3 | 99±2 | 89±7 |
| | 1 | 104±8 | 78±2 | 98±3 | 96±6 |
| 10 | 2 | 104±4 | 73±3 | 95±1 | 96±1 |
| | 3 | 104±2 | 78±4 | 97±3 | 97±4 |
| | 4 | 100±2 | 74±10 | 93±4 | 96±4 |
| | 7 | 108±5 | 72±4 | 96±2 | 94±2 |
| | 9 | 102±3 | 66±3 | 92±3 | 93±2 |
| 15 | 12 | 101±2 | 66±1 | 89±2 | 92±5 |

Each data point represents the mean ± relative standard deviation of three individual samples taken from three separate vials.

EXAMPLE 4

Preparation of Reservoirs Release Rate Profiles

Titanium reservoir systems of implantable drug delivery devices (as disclosed in U.S. Patent Application Serial No. 08/595,761, incorporated herein by reference) were each assembled with an osmotic engine, piston, and rate controlling membrane. The reservoirs were filled with the appropriate amount of viscous vehicle formulation and capped with a flow plug. The systems were placed in a water bath at 37°C, and allowed to release formulation for an extended period of time. Released material was sampled twice per week. Assays for released material were completed using reverse phase HPLC. The resulting concentrations of beneficial agent for each system were converted to released amount per day. The beneficial

agent was found to have a zero order release from the implantable drug delivery device. As shown in Figures 3 through 8.

EXAMPLE 5

5 Stability of hGH in Non-aqueous Viscous Vehicle Formulations

Formulations of 10% w/w hGH in vehicle were prepared as described above and placed in vials. The formulations were subjected to accelerated aging by storing them at elevated temperatures and times shown in the below
10 table in a controlled temperature oven .

TABLE 7

| | Vehicle | Time(hrs) | Temperature | %LS by SEC | %LS by RP-HPLC |
|----|--------------|-----------|-------------|------------|----------------|
| | Pluronic 105 | 0 | 50°C | 98±3 | 101±3 |
| | Pluronic 105 | 1 | 50°C | 98±3 | 101±4 |
| 15 | Pluronic 105 | 2 | 50°C | 100±1 | 102±3 |
| | Pluronic 105 | 4 | 50°C | 101±3 | 105±3 |
| | GML/LL/PVP | 0 | 65°C | 99±3 | 101±3 |
| | GML/LL/PVP | 1 | 65°C | 93±6 | 97±6 |
| | GML/LL/PVP | 2 | 65°C | 91±5 | 95±5 |
| 20 | GML/LL/PVP | 4 | 65°C | 95±3 | 98±3 |

Each data point represents the mean \pm relative standard deviation of three individual samples taken from three separate vials.

25 Results, presented in the following table, demonstrate that these formulations were able to maintain the stability of the hGH in each case. In each case, at least 70% hGH was retained.

TABLE 8
RECOVERY OF hGH FROM NONAQUEOUS SUSPENSIONS

| | <u>Vehicle</u> | <u>%LS by RP-HPLC</u> | <u>%LS by Size-exclusion HPLC</u> |
|---|----------------|-----------------------|-----------------------------------|
| 5 | PVP/PEG 400 | 99±3% | 88±6% |
| | GML/LL/PVP | 99±2% | 92±2% |
| | Pluronic 105 | 89±7% | 87±7% |

Each data point represents the mean ± relative standard deviation of three individual samples taken from three separate vials.

%LS or % label strength = (measured protein content + theoretical protein content) x 100%

EXAMPLE 6

15 A. Preparation by Spray Drying

GLP-1 (Polypeptide Laboratories, Wofenbuttel, Germany) was obtained as an acetate salt and was lyophilized. The lyophilized GLP-1 was dissolved in purified water at 19.9 mg/ml and spray dried using a Yamato mini-spray dryer. The spray drying parameters were: 120°C inlet temperature, 20 90°C outlet temperature, solution flow rate 3.3-5.3 ml/min. Powder was collected in a collection vessel through a cyclone trap. All handling of the spray dried powder took place in a dry box evacuated with nitrogen (% RH: 1-4%).

B. Preparation of GLP-1 Formulation

25 A portion of the single phase viscous vehicle was weighed and heated to 60°C. GLP-1 (Polypeptide Laboratories, Wolfenbuttel, Germany) was added 27% w/w to the vehicle and mixed for 15 minutes. The mixing was completed under vacuum to remove air bubbles.

The resulting suspension was dissolved in 10 ml of release rate buffer and analyzed by size exclusion and reverse-phase chromatography.

30 C. Analysis of GLP-1 Formulations

The reverse-phase HPLC method consisted of a C-8 5 μ , 4.6 x 250 mm analytical column (Higgins Analytical, Mountain View, CA) with detection at 210 nm. A step gradient method from 25% B to 80% B at 1 ml/min was as follows: 0-5 min at 25% B, 5-30 min at 25-50% B, 30-35 min at 50-80% B.

5 Mobile phase A was 0.1% TFA in water and mobile phase B was 0.1% TFA in acetonitrile. The formulations were found to be stable for 6 months.

The size exclusion chromatography method consisted of a Pharmacia FPLC HR 10/30 column at a flow rate of 0.5 ml/min. An isocratic method was employed, where the mobile phase was 100 mM ammonium phosphate, 200 mM sodium chloride, pH 2.0, and peptide was detected at 210 nm. The
10 formulations were found to be stable for 6 months.

D. Preparation of Reservoirs

Titanium reservoir systems of implantable drug delivery devices (as disclosed in U.S. Patent Application Serial No. 08/595,761, incorporated
15 herein by reference) were each assembled with an osmotic engine, piston, and rate controlling membrane. The reservoirs were filled with the appropriate amount of viscous vehicle formulation and capped with a flow plug. The systems were placed in a water bath at 37°C, and allowed to release formulation for an extended period of time. Released material was
20 sampled twice per week. Assays for released material were completed using reverse phase HPLC. The resulting concentrations of beneficial agent for each system were converted to release amount per day. The beneficial agent was found to have a zero order release from the implantable drug delivery device.

25 Modification of the above-described modes of carrying out various embodiments of this invention will be apparent to those of skill in the art following the teachings of this invention as set forth herein. The examples described above are not limiting, but are merely exemplary of this invention, the scope of which is defined by the following claims.

Claims:

1. A stable non-aqueous single phase biocompatible viscous vehicle capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.
2. The vehicle of claim 1 comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type.
3. The vehicle of claim 1 comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type.
4. The vehicle of claim 1 which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type.
5. The vehicle of claim 2 or 4 wherein said solvent is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols.
6. The vehicle of claim 2 or 4 wherein said surfactant is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.
7. The vehicle of claim 2 or 4 wherein said polymer is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

8. The vehicle of claim 2 wherein the ratios of the components are in the range of 40:60 to 60:40.

5 9. The vehicle of claim 4 wherein the ratios of the components are in the range of about 5% to about 60% for solvent, about 5% to about 40% for surfactant, and about 5% to about 60% for polymer.

10 10. The vehicle of claim 4 wherein the polymer is polyvinylpyrrolidone, the surfactant is gml, and the solvent is lauryl lactate.

11. The vehicle of claim 10 wherein the ratios of the components are in the range of about 35% to about 45% for solvent, about 5% to about 15% for surfactant, and about 50% to about 55 % for polymer,

15 12. The vehicle of claim 4 wherein the polymer is polyvinylpyrrolidone, the surfactant is polysorbate, and the solvent is lauryl lactate.

20 13. The vehicle of claim 4 wherein the polymer is poly(D,L-lactide), the surfactant is a Pluronic block copolymer, and the solvent is propylene carbonate.

25 14. The vehicle of claim 4 wherein the polymer is polyvinylpyrrolidone, the surfactant is myristyl lactate, and the solvent is lauryl alcohol.

15. The vehicle of claim 1 which comprises an antioxidant.

30 16. The vehicle of claim 15 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.

17. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

5

18. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and
10 1×10^{-7} reciprocal second.

19. The formulation of claim 17 wherein said formulation is stable at body temperature for extended periods of time.

15 20. The formulation of claim 17 which comprises at least about 0.1% (w/w) beneficial agent.

21. The formulation of claim 17 which comprises at least about 10% (w/w) beneficial agent.

20

22. The formulation of claim 17 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.

25 23. The formulation of claim 22 wherein said beneficial agent is a protein.

24. The formulation of claim 17 which is stable at 65° C for at least about 2 months.

30 25. The formulation of claim 17 which is stable at 37° C for at least about 3 months.

26. The formulation of claim 17 which is stable at 37° C for at least about one year.

27. The formulation of claim 17 which is adapted for use in an implantable drug delivery device.

28. The formulation of claim 17 wherein said vehicle is selected from the group consisting of solvent, surfactant and polymer.

29. The formulation of claim 17 wherein said vehicle comprises an antioxidant.

30. The formulation of claim 17 comprising a beneficial agent which has been dried to a low moisture content prior to incorporation in said formulation.

31. The formulation of claim 17 which is stable after sterilization.

32. A method for preparing the stable single phase viscous vehicle of claim 1 comprising the steps of (1) blending the ingredients at elevated temperature under dry conditions to allow them to liquify, and (2) allowing the liquid from step (1) to cool to room temperature.

33. A method for preparing the stable formulation of claim 17 comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

34. The method of claim 33 wherein at least about 0.1% (w/w) beneficial agent is suspended in said vehicle.

35. The method of claim 33 wherein at least about 10% (w/w) beneficial agent is suspended in said vehicle.

5 36. A method for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent comprising administering to said subject a therapeutically effective amount of the formulation of Claim 17.

37. The method of claim 36 wherein said administration is parenteral administration.

10

38. The method of claim 36 wherein said administration is long-term continuous administration.

15

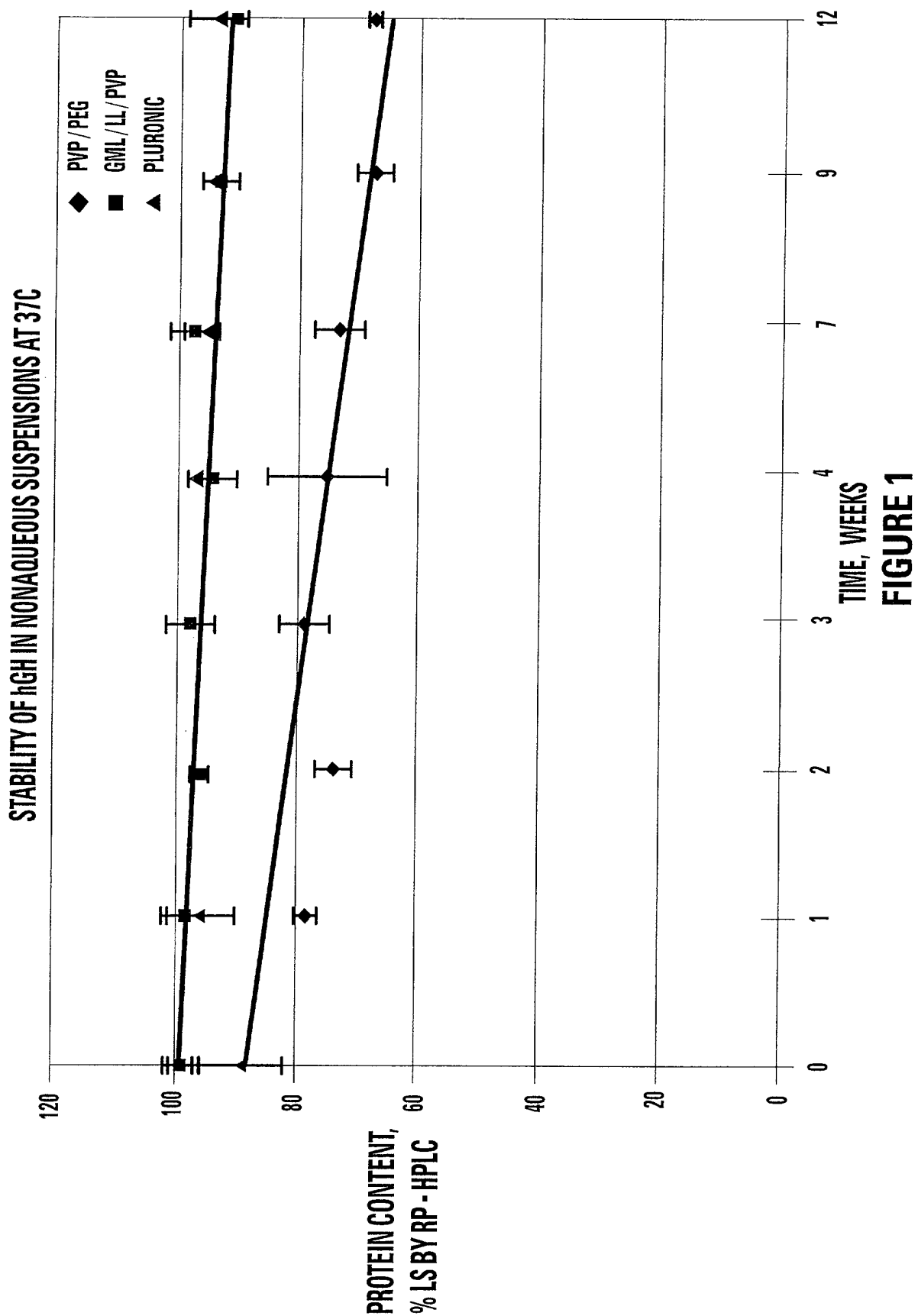
39. The method of claim 36 wherein said administration is accomplished by use of an implantable drug delivery system.

20

40. The method of claim 36 wherein said daily administration continues for a period selected from the group consisting of about 3 months, about 6 months, and about 12 months.

41. The method of claim 40 wherein said daily administration is accomplished using an implantable drug delivery system.

10



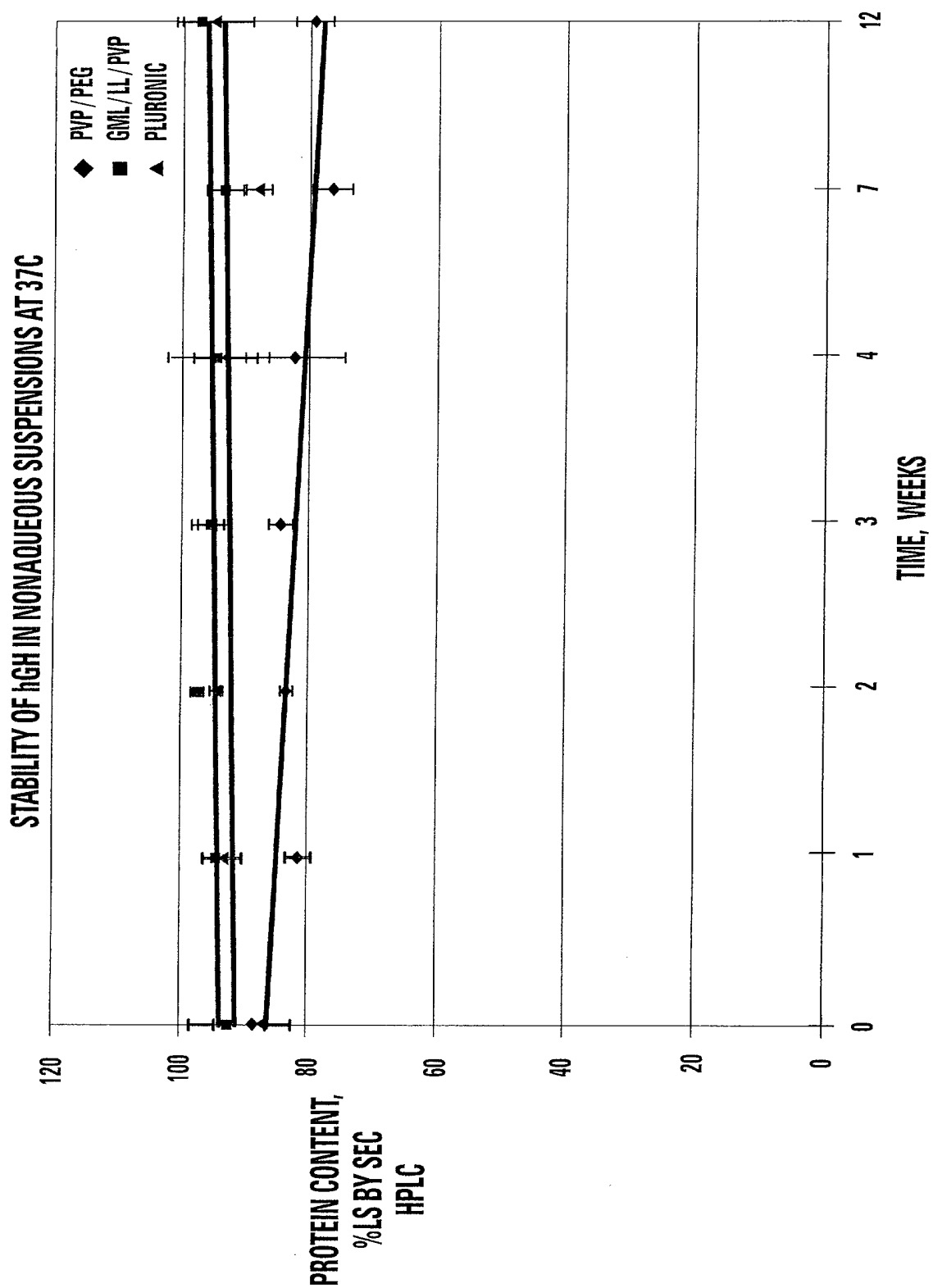


FIGURE 2

**AVERAGE RELEASE RATE
10% wt/wt SPRAY DRIED LYSOZYME
IN SUSPENSION VEHICLES**

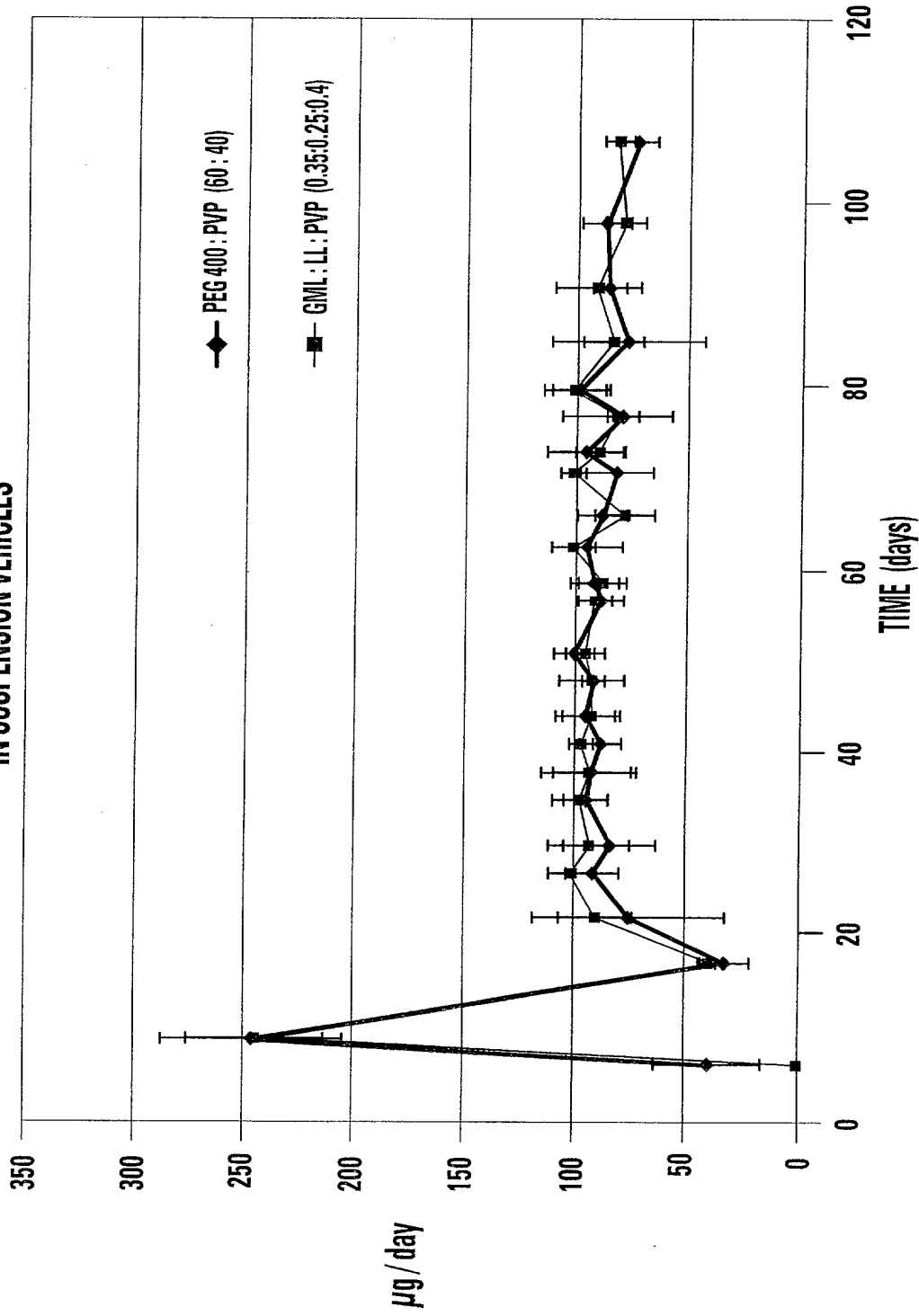


FIGURE 3

IN VITRO SYSTEMS, PRE RAT STUDY
AVERAGE RELEASE RATE ($\mu\text{g/day}$)

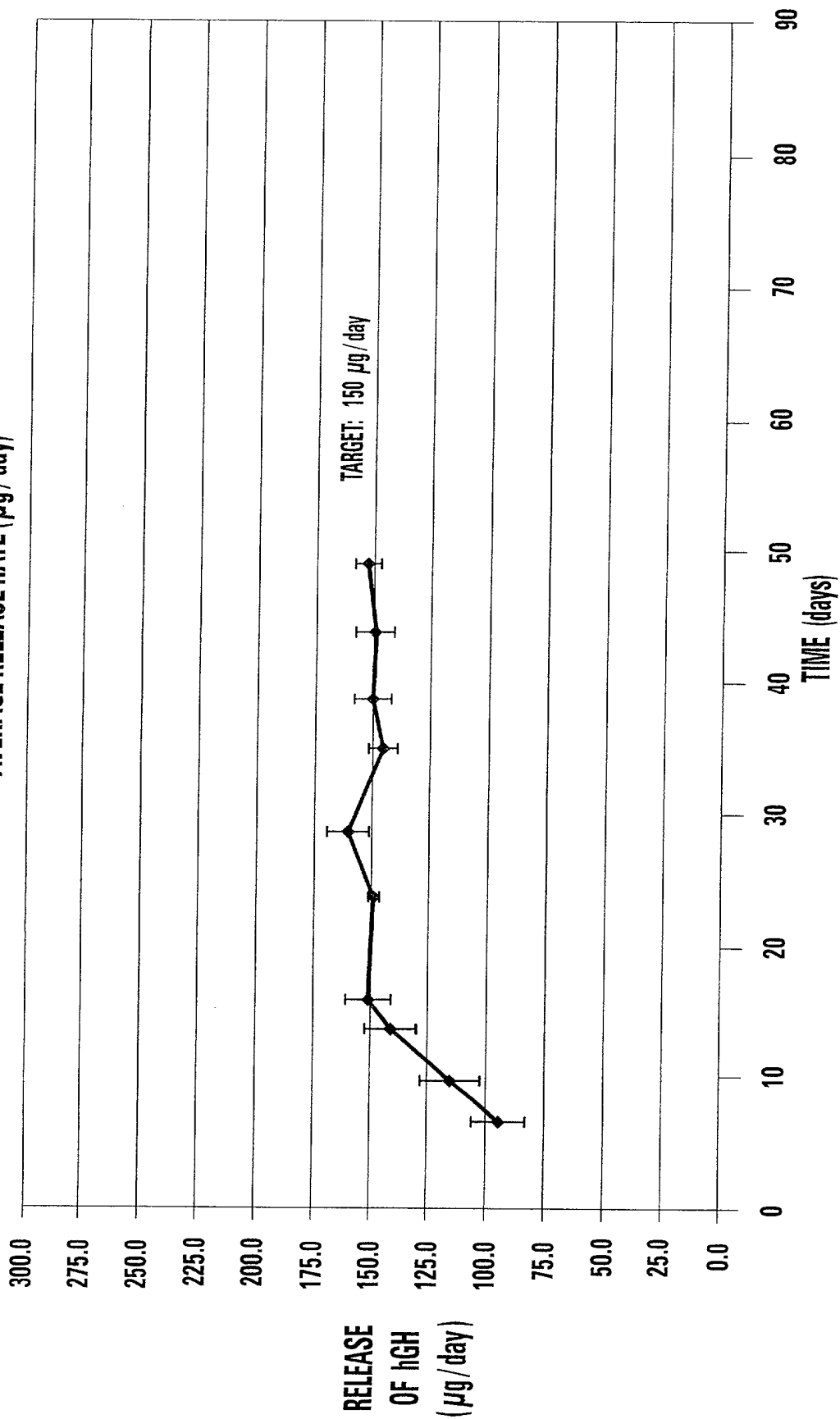


FIGURE 4

AVERAGE RELEASE RATE PROFILE FOR 10% LYSOZYME IN LA/PVP (40/60)

TARGET = 150 $\mu\text{g/day}$

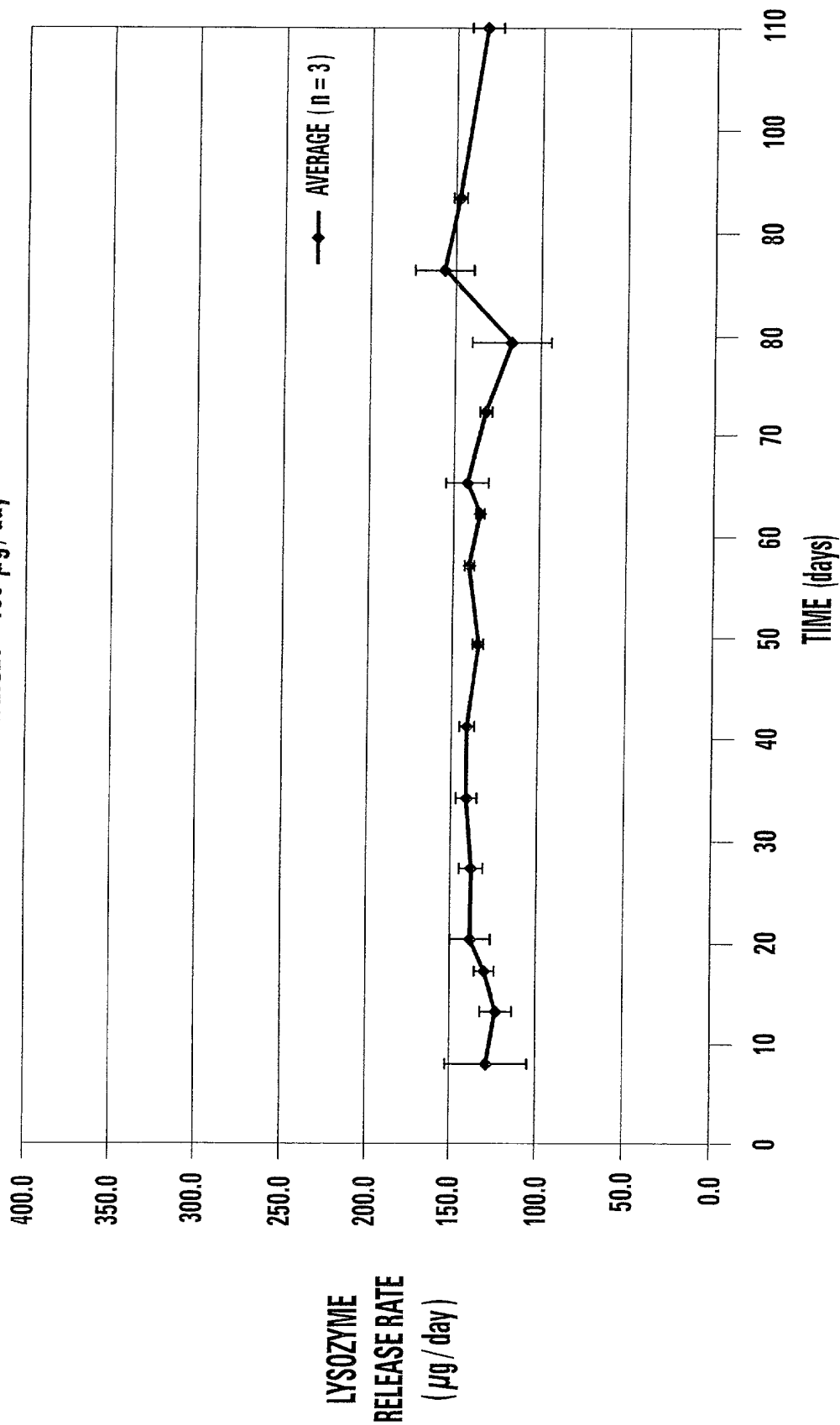


FIGURE 5

25% LOADED PARTICLES IN GML:LL:PVP VEHICLE
RELEASE RATE ($\mu\text{g/day}$), $n=5$

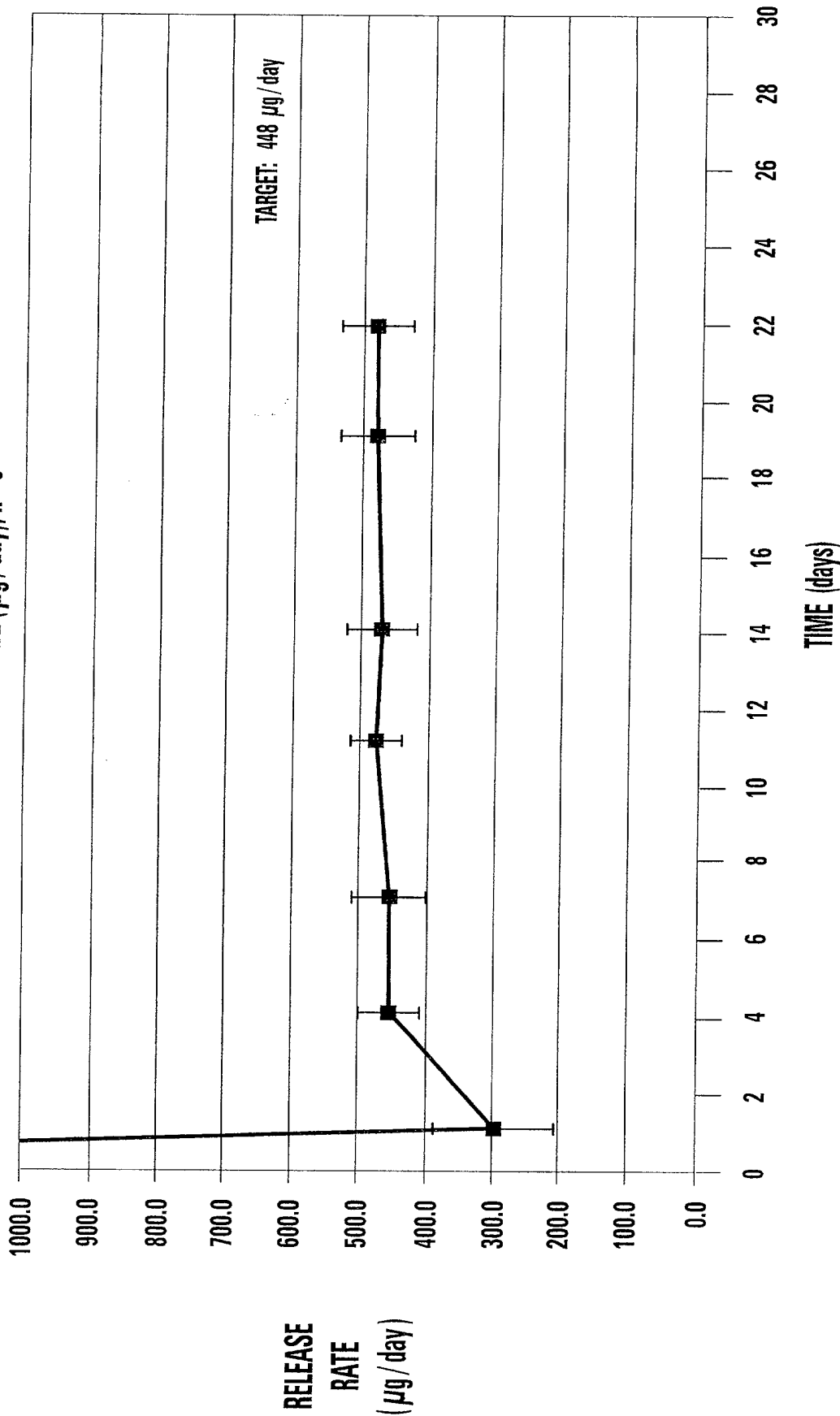


FIGURE 6

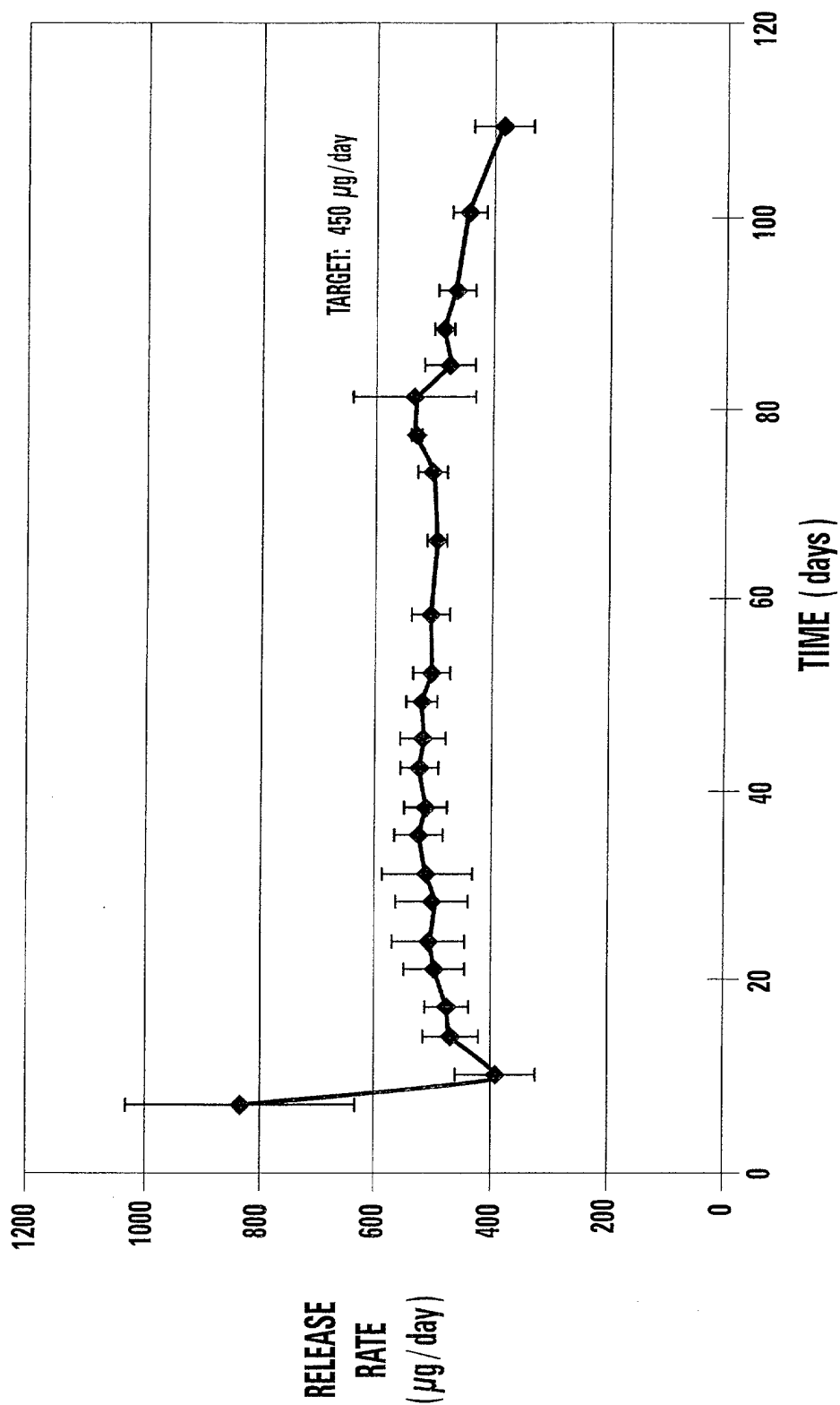


FIGURE 7

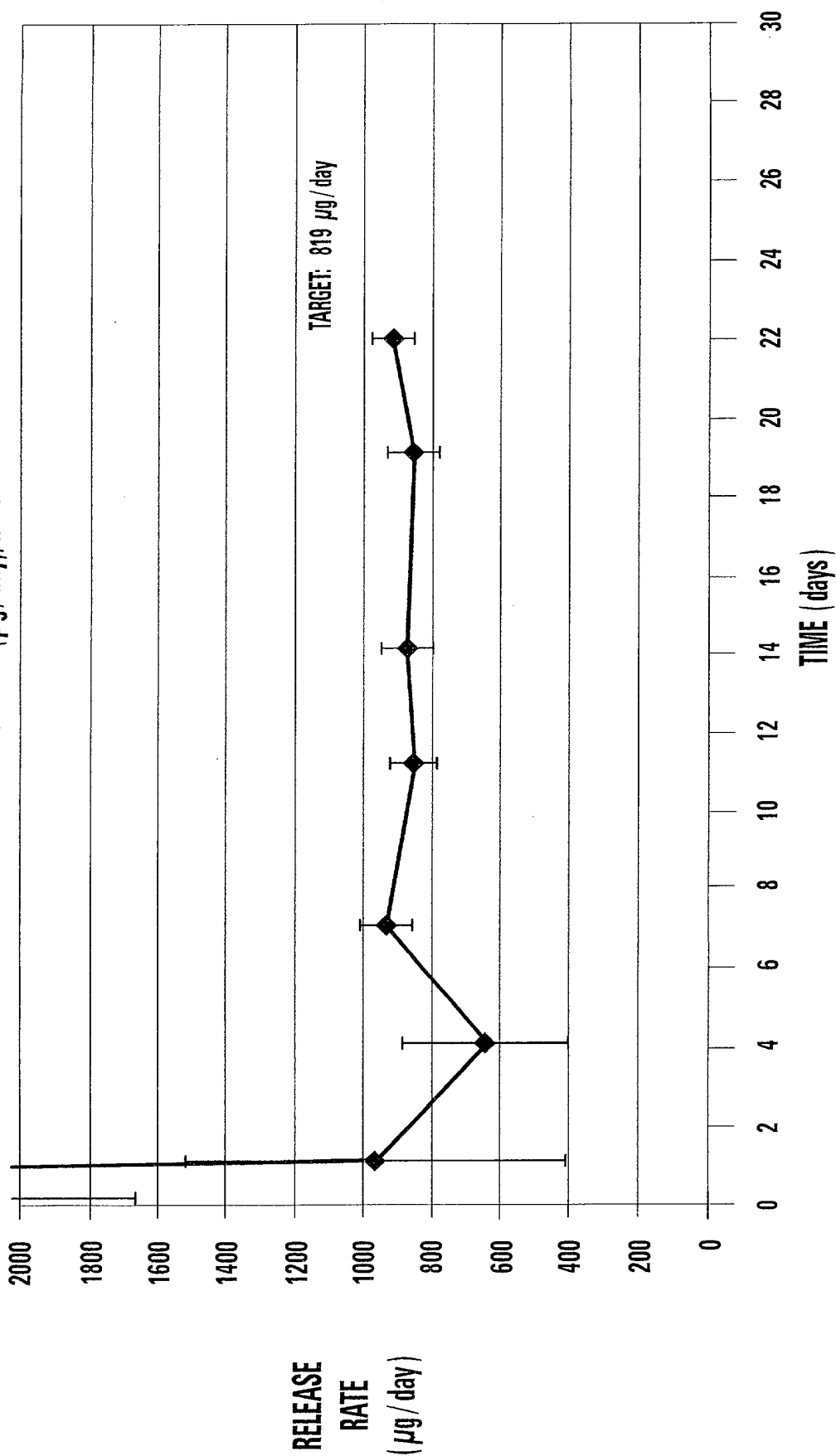


FIGURE 8

Docket No.
ARC2914C1

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

STABLE NON-AQUEOUS SINGLE PHASE VISCOUS VEHICLES AND FORMULATIONS UTILIZING SUCH VEHICLES

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

(Application Serial No.)

(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Owen Bates

Registration No.: 40,436

Pauline A. Clarke

Registration No.: 29,783

John A. Dhuey

Registration No.: 26,265

D. Byron Miller

Registration No.: 30,661

Paul B. Simboli

Registration No.: 38,616

Steven F. Stone

Registration No.: 20,246

Send Correspondence to: **Pauline A. Clarke**
ALZA Corporation
1900 Charleston Road, Bldg. M10-3, P.O. Box 7210
Mountain View, California 94039-7210

Direct Telephone Calls to: *(name and telephone number)*

Pauline A. Clarke 650-564-5560

Full name of sole or first inventor

Stephen A. Berry

Sole or first inventor's signature

Date

Residence

1050 Spring Road Grove, Hollister, CA 95023

Citizenship

USA

Post Office Address

Full name of second inventor, if any

Pamela J. Ferreira

Second inventor's signature

Date

Residence

304 Canoe Court, Redwood City, CA 94065

Citizenship

USA

Post Office Address

| | |
|--|------|
| Full name of third inventor, if any Houdin Dehnad | |
| Third inventor's signature | Date |
| Residence 507 Vallejo Street, El Granada, CA 94018 | |
| Citizenship Iran | |
| Post Office Address | |
| | |

| | |
|---|------|
| Full name of fourth inventor, if any Anna Muchnik | |
| Fourth inventor's signature | Date |
| Residence 1542 Winding Way, Belmont, CA 94002 | |
| Citizenship USA | |
| Post Office Address | |
| | |

| | |
|-------------------------------------|------|
| Full name of fifth inventor, if any | |
| Fifth inventor's signature | Date |
| Residence | |
| Citizenship | |
| Post Office Address | |
| | |

| | |
|-------------------------------------|------|
| Full name of sixth inventor, if any | |
| Sixth inventor's signature | Date |
| Residence | |
| Citizenship | |
| Post Office Address | |
| | |